Supplementary Materials for "Potential impact of spatially targeted adult tuberculosis vaccine in Gujarat, India."

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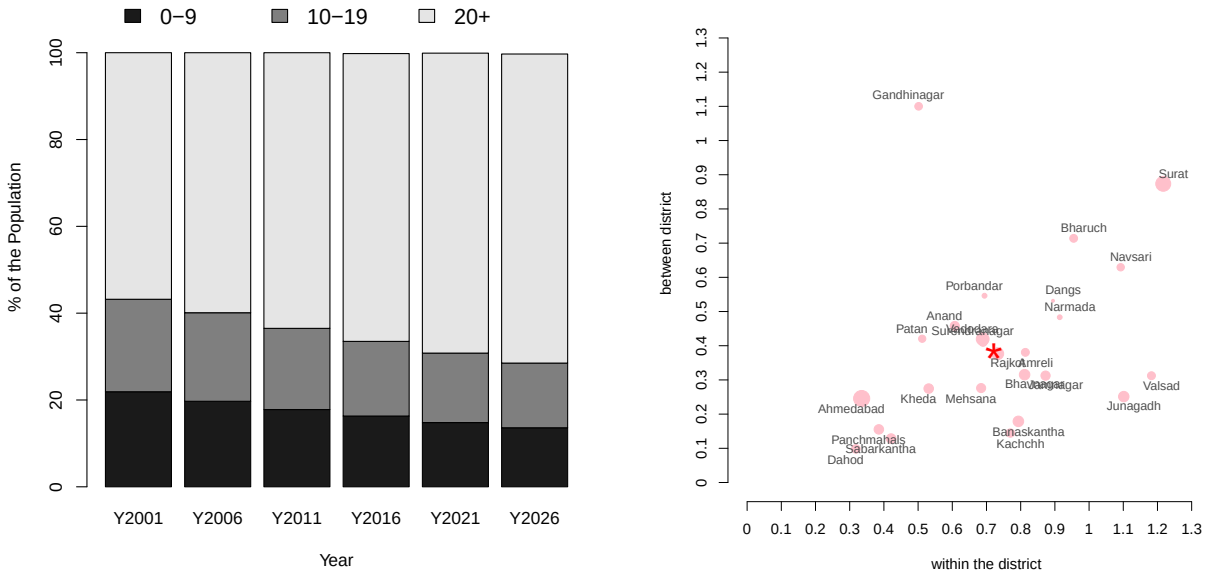

Figure S-1: Demography and migration pattern in Gujarat. [Left] Shown are age distributions of the population of Gujarat based on the 2001 census. Distributions for years between 2006 and 2026 are based on projections from the 2001 census data. [Right] Shown are annual migration rates in district of Gujarat, based on the 2001 census. Plotted on vertical axis are the percentages of district populations that migrated from outside of the district within the year, and plotted on the vertical axis are the percentages of the district populations that migrated from within the district within the year. The red star represents the average annual rates of migration (∼0.7% within the district and ∼0.4% between the district).

Supplementary data: Demography & Migration

Data on demography were collated from the 2001 census of Gujarat [1]. We used the projected age-distribution of the population of Gujarat [2], shown in Fig. S-1[Left], for 2011 as the baseline population for the model. This resulted in a population with percentages in the age groups 0-9 years, 10-19 years, and 20 years and above to be 17.8%, 18.7%, and 63.5%, respectively. Data on migration patterns in Gujarat were also collated from the 2001 census of Gujarat [3]. As detailed in Fig. S-1[Right], the annual migration rate in Gujarat (averaged over all districts) was approximately 1.1%, of which 0.7% represented migration between different districts of Gujarat and 0.4% were within the districts. Assuming that such migration is equivalent across boundaries of the "hotspot" (i.e., that 90% of recent migrants in the hotspot—which accounts for 10% of the population—immigrated from outside the hotspot), we assumed in the base case that 1% of the population of the hotspot had migrated from the general population in the past year, and that 0.1% of the general population had migrated from the hotspot.

Supplementary data: Variability in high incidence "hotspots".

The geographic heterogeneity in TB incidence, measured at the level of TB Units, in Gujarat was stable over the 14 quarters which spanned from first quarter of 2009 to second quarter of 2012. TB incidence in the TB units with TB incidence in the highest decile (Fig. S-2[Left], red line) were consistently between 1.5 to 1.7 times larger than the incidence in the remaining population (Fig. S-2[Left], blue line). TB incidence in the "hotspot" TUs (TUs picked on the basis of average TB incidence over the 14 quarters, shown by the dashed line) closely resembled the TB incidence in the TB units with TB incidence in the highest decile each quarter. Furthermore, most of the TB Units that comprised the "hotspots" consistently featured among the TB units with TB in the

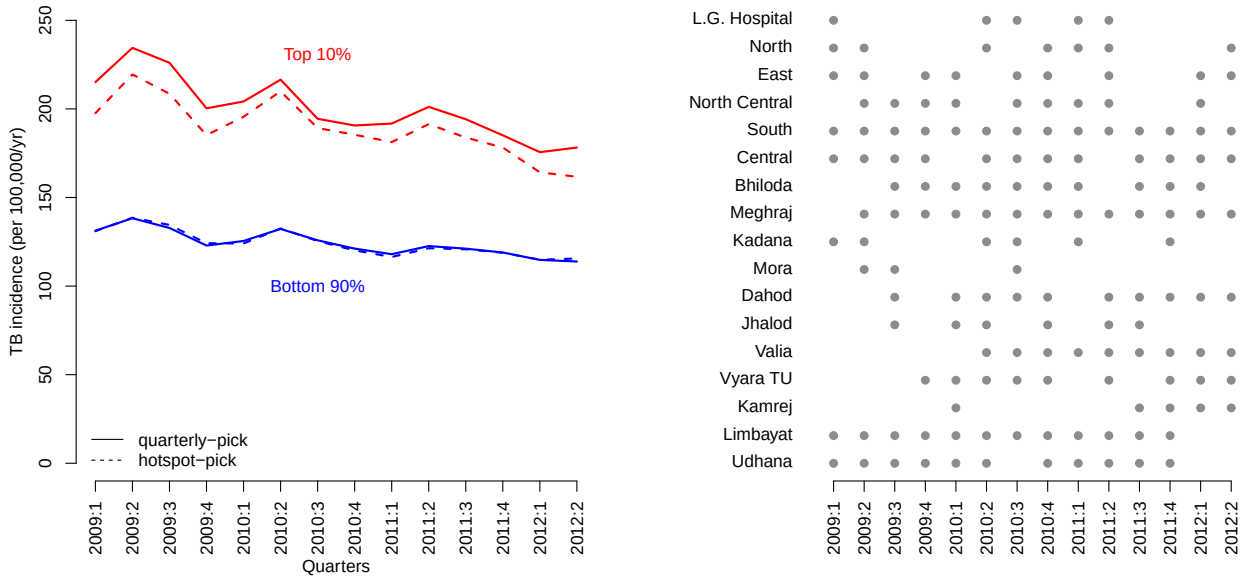

Figure S-2: [Left] Shown are the trends in TB incidence in the TB units with TB incidence in the highest decile, (in red) and rest of the population (in blue). The solid lines show pick based on the quarterly incidence, and dashed lines show the "hotspot" TUs which were based the average in all 14 quarters. [Right] For each of the TB units picked, quarters marked with a dot are when the TB incidence were in the highest decile for the specific quarter.

top 10% (Fig. S-2[Right]), indicating that regions of high TB incidence were quite stable.

Details of demonstration study

The demonstration study was conducted in November and December of 2013. We picked 5 Gujarati TB units: East in Ahmadabad, Halol in Panch Mahals, and Hirabaug in Surat were locations with relatively high TB incidence; and Jetpur in Rajkot and Keshod in Junagadh were locations with relatively low TB incidence (Fig. S-2). Within each TU, we randomly selected 3 designated microscopy centers (DMC) to conduct our demonstration study. The selected DMCs are presented in table 2 in the main text. The demonstration study consisted of:

1. Following patients referred to the TB lab by the outpatient department for sputum examination to lab registration for a day.
2. Comparing registered new smear positive TB cases between lab register and TB register during the third quarter of 2013.
3. Comparing TB case counts between monthly lab abstract and the lab register during the same time period.
4. Comparing TB case counts between the TB register and the case finding report (TU level) during the same time period.
5. Comparing TB case counts between the lab register and the PHI report during the same time period

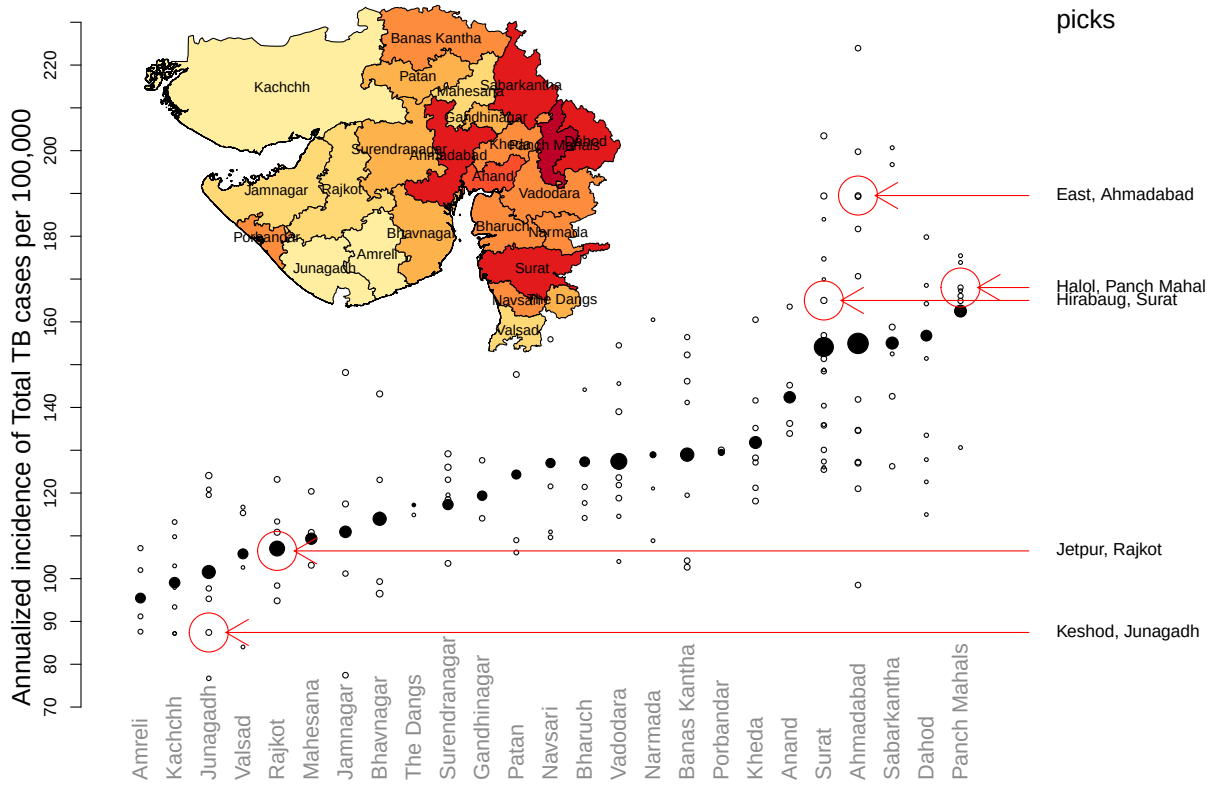

Figure S-3: Gujarati TB units picked for the demonstration study. We picked 5 Gujarati TB units for the demonstrations study: East in Ahmadabad, Halol in Panch Mahals, and Hirabaug in Surat were locations with relatively high TB incidence; and Jetpur in Rajkot and Keshod in Junagadh were locations with relatively low TB incidence.

Model details

The model we developed to evaluate the effect of spatially targeted vaccine was structured to take into account four important factors: (i) spatial heterogeneity of TB; (ii) transmission dynamics of TB; (iii) aging of the population; and (iv) vaccine derived protection. The model is described and schematically presented in the main text. Here, we provide the mathematical expressions of the ordinary differential equations that describe the model in the entirety. Let $X_{\{i,j,k,l\}}$ be the number of individuals with TB status i; where $i \in \{\text{Uninfected}, \text{LTBI}, \text{Active TB}\}$, living in TB zone j; where $j \in \{\text{hotspot}, \text{general population}\}$, with vaccine status k, where $k \in \{\text{unvaccinated}, \text{vaccine} \leq 1, \ldots, \text{vaccine} \leq 10, \text{vaccine} > 10\}$; and in age group l; where $l \in \{0-9, 10-19, 20+\}$. Let the forces of infection generated in hotspot and the general population, be $\lambda_h = \beta_h \sum_k \sum_l X_{\{i=\text{Active TB}, j=\text{hotspot}, k, l\}}$ and $\lambda_l = \beta_l \sum_k \sum_l X_{\{i=\text{Active TB}, j=\text{general population}, k, l\}}$, respectively. We present the differential equations to describe transitions in various populations/compartments, by describing the mechanisms behind the transitions. We present equations for "uninfected", "LTBI" (latently infected), and "Active TB" (infectious with active TB disease) populations sequentially. The differences within these populations are pointed out via "if" conditions. If there are no "if" clause associated with a transition, then it is applicable for all populations. The symbol/shorthand notations used in the equations are shown in Table S-1.

$$\frac{\mathrm{d}X_{\{i=\text{Uninfected},j,k,l\}}}{\mathrm{d}t} =$$

births:

if $l \in \{0-9\}$ and if $k \in \{\text{unvaccinated}\}$ $+ \mu \sum_{\substack{i \neq \\ \text{Active TB}}} \sum_k \sum_l X_{\{i,j,k,l\}} + \mu_A \sum_k \sum_l X_{\{i=\text{Active TB},j,k,l\}}$

deaths:

$- \mu\, X_{\{i,j,k,l\}}$

new infections:

if $k \in \{\text{unvaccinated}, \text{vaccine} > 10\}$ and if $j \in$ hotspot $- [\lambda_h + \sigma\, \lambda_l]\, X_{\{i,j,k,l\}}$

if $k \in \{\text{vaccine} \leq 1, \ldots, \text{vaccine} \leq 10\}$ and if $j \in$ hotspot $- [\lambda_h + \sigma\, \lambda_l]\, X_{\{i,j,k,l\}}$

if $k \in \{\text{unvaccinated}, \text{vaccine} > 10\}$ and if $j \in$ general population $- [\lambda_l + \sigma\, \lambda_h]\, X_{\{i,j,k,l\}}$

if $k \in \{\text{vaccine} \leq 1, \ldots, \text{vaccine} \leq 10\}$ and if $j \in$ general population $- [\lambda_l + \sigma\, \lambda_h]\, X_{\{i,j,k,l\}}$

aging and continuous vaccination [*]**:**

if $l \in \{0-9\}$ $- 0.1\, X_{\{i,j,k,l\}}$

if $l \in \{10-19\}$ and $k \in \{\text{unvaccinated}\}$ $- 0.1\, X_{\{i,j,k,l=10-19\}} + 0.1\, (1 - \nu_{\text{coverage:V-10}})\, X_{\{i,j,k,l=0-9\}}$

if $l \in \{10-19\}$ and $k \in \{\text{vaccine} \leq 1\}$ $- 0.1\, X_{\{i,j,k,l=10-19\}} + 0.1\, \nu_{\text{coverage:V-10}}\, X_{\{i,j,k,l=0-9\}}$

if $l \in \{20+\}$ $+ 0.1\, X_{\{i,j,k,l=0-9\}}$

vaccine immunity [†]**:**

if $k \in \{\text{vaccine} \leq 1\}$ $- X_{\{i,j,k,l\}}$

if $k \in \{\text{vaccine} \leq 2, \ldots, \text{vaccine} \leq 10\}$ $+ X_{\{i,j,k-1,l\}} - X_{\{i,j,k,l\}}$

if $k \in \{\text{vaccine} > 10\}$ $+ X_{\{i,j,k-1,l\}}$

migration:

if $j \in \{\text{hotspot}\}$ $- m\, X_{\{i,j,k,l\}} + m\, \frac{N_h}{N_l}\, X_{\{i,j=\text{general population},k,l\}}$

if $j \in \{\text{general population}\}$ $+ m\, X_{\{i,j=\text{hotspot},k,l\}} - m\, \frac{N_h}{N_l}\, X_{\{i,j,k,l\}}$

[*]the rates of 0.1/year represent average transition rates from 10 year age compartments.
[†]the rates of 1/year represent average transition rates from 1 year immune compartments.

$$\frac{\mathrm{d}X_{\{i=\text{LTBI},j,k,l\}}}{\mathrm{d}t} =$$

deaths:

$$- \mu\, X_{\{i,j,k,l\}}$$

new infections:

if $k \in \{\text{unvaccinated}, \text{vaccine} > 10\}$ and if $j \in$ hotspot
$$+ [1-p]\,[\lambda_h + \sigma\,\lambda_l]\, X_{\{i=\text{Uninfected},j,k,l\}}$$

if $k \in \{\text{vaccine} \leq 1, \ldots, \text{vaccine} \leq 10\}$ and if $j \in$ hotspot
$$+ [(1-p) + p\,[1-\nu_{\text{efficacy}}]]\,[\lambda_h + \sigma\,\lambda_l]\, X_{\{i=\text{Uninfected},j,k,l\}}$$

if $k \in \{\text{unvaccinated}, \text{vaccine} > 10\}$ and if $j \in$ general population
$$+ [1-p]\,[\lambda_l + \sigma\,\lambda_h]\, X_{\{i=\text{Uninfected},j,k,l\}}$$

if $k \in \{\text{vaccine} \leq 1, \ldots, \text{vaccine} \leq 10\}$ and if $j \in$ general population
$$+ [(1-p) + p\,[1-\nu_{\text{efficacy}}]]\,[\lambda_l + \sigma\,\lambda_h]\, X_{\{i=\text{Uninfected},j,k,l\}}$$

reinfections:

if $k \in \{\text{unvaccinated}, \text{vaccine} > 10\}$ and if $j \in$ hotspot
$$- p\,\xi\,[\lambda_h + \sigma\,\lambda_l]\, X_{\{i,j,k,l\}}$$

if $k \in \{\text{vaccine} \leq 1, \ldots, \text{vaccine} \leq 10\}$ and if $j \in$ hotspot
$$- p\,\xi\,[1-\nu_{\text{efficacy}}]\,[\lambda_h + \sigma\,\lambda_l]\, X_{\{i,j,k,l\}}$$

if $k \in \{\text{unvaccinated}, \text{vaccine} > 10\}$ and if $j \in$ general population
$$- p\,\xi\,[\lambda_l + \sigma\,\lambda_h]\, X_{\{i,j,k,l\}}$$

if $k \in \{\text{vaccine} \leq 1, \ldots, \text{vaccine} \leq 10\}$ and if $j \in$ general population
$$- p\,\xi\,[1-\nu_{\text{efficacy}}]\,[\lambda_l + \sigma\,\lambda_h]\, X_{\{i,j,k,l\}}$$

reactivation:

if $k \in \{\text{unvaccinated}, \text{vaccine} > 10\}$
$$- \phi\; X_{\{i,j,k,l\}}$$

if $k \in \{\text{vaccine} \leq 1, \ldots, \text{vaccine} \leq 10\}$
$$- [1-v_{\text{efficacy}}]\,\phi\; X_{\{i,j,k,l\}}$$

treatment:

$$+ [1-k]\,\omega\, X_{\{i=\text{Active TB},j,k,l\}}$$

aging and continuous vaccination:

if $l \in \{0-9\}$
$$- 0.1\, X_{\{i,j,k,l\}}$$

if $l \in \{10-19\}$ and $k \in \{\text{unvaccinated}\}$
$$- 0.1\, X_{\{i,j,k,l=10-19\}} + 0.1\,(1-\nu_{\text{coverage:V-10}})\, X_{\{i,j,k,l=0-9\}}$$

if $l \in \{10-19\}$ and $k \in \{\text{vaccine} \leq 1\}$
$$- 0.1\, X_{\{i,j,k,l=10-19\}} + 0.1\,\nu_{\text{coverage:V-10}}\, X_{\{i,j,k,l=0-9\}}$$

if $l \in \{20+\}$
$$+ 0.1\, X_{\{i,j,k,l=0-9\}}$$

vaccine immunity:

if $k \in \{\text{vaccine} \leq 1\}$
$$- X_{\{i,j,k,l\}}$$

if $k \in \{\text{vaccine} \leq 2, \ldots, \text{vaccine} \leq 10\}$
$$+ X_{\{i,j,k-1,l\}} - X_{\{i,j,k,l\}}$$

if $k \in \{\text{vaccine} > 10\}$
$$+ X_{\{i,j,k-1,l\}}$$

migration:

if $j \in \{\text{hotspot}\}$
$$- m\, X_{\{i,j,k,l\}} + m\,\frac{N_h}{N_l}\, X_{\{i,j=\text{general population},k,l\}}$$

if $j \in \{\text{general population}\}$
$$+ m\, X_{\{i,j=\text{hotspot},k,l\}} - m\,\frac{N_h}{N_l}\, X_{\{i,j,k,l\}}$$

$$\frac{\mathrm{d}X_{\{i=\text{Active TB},j,k,l\}}}{\mathrm{d}t} =$$

deaths:

$$- \mu_A \, X_{\{i,j,k,l\}}$$

new infections:

$$\text{if } k \in \{\text{unvaccinated}, \text{vaccine} > 10\} \text{ and if } j \in \text{hotspot} \quad + p\,[\lambda_h + \sigma\,\lambda_l]\,X_{\{i=\text{Uninfected},j,k,l\}}$$

$$\text{if } k \in \{\text{vaccine} \leq 1, \ldots, \text{vaccine} \leq 10\} \text{ and if } j \in \text{hotspot} \quad + p\,[1-\nu_{\text{efficacy}}]\,[\lambda_h + \sigma\,\lambda_l]\,X_{\{i=\text{Uninfected},j,k,l\}}$$

$$\text{if } k \in \{\text{unvaccinated}, \text{vaccine} > 10\} \text{ and if } j \in \text{general population} \quad + p\,[\lambda_l + \sigma\,\lambda_h]\,X_{\{i=\text{Uninfected},j,k,l\}}$$

$$\text{if } k \in \{\text{vaccine} \leq 1, \ldots, \text{vaccine} \leq 10\} \text{ and if } j \in \text{general population} \quad + p\,[1-\nu_{\text{efficacy}}]\,[\lambda_l + \sigma\,\lambda_h]\,X_{\{i=\text{Uninfected},j,k,l\}}$$

reinfections:

$$\text{if } k \in \{\text{unvaccinated}, \text{vaccine} > 10\} \text{ and if } j \in \text{hotspot} \quad + p\,\xi\,[\lambda_h + \sigma\,\lambda_l]\,X_{\{i=\text{LTBI},j,k,l\}}$$

$$\text{if } k \in \{\text{vaccine} \leq 1, \ldots, \text{vaccine} \leq 10\} \text{ and if } j \in \text{hotspot} \quad + p\,\xi\,[1-\nu_{\text{efficacy}}]\,[\lambda_h + \sigma\,\lambda_l]\,X_{\{i=\text{LTBI},j,k,l\}}$$

$$\text{if } k \in \{\text{unvaccinated}, \text{vaccine} > 10\} \text{ and if } j \in \text{general population} \quad + p\,\xi\,[\lambda_l + \sigma\,\lambda_h]\,X_{\{i=\text{LTBI},j,k,l\}}$$

$$\text{if } k \in \{\text{vaccine} \leq 1, \ldots, \text{vaccine} \leq 10\} \text{ and if } j \in \text{general population} \quad + p\,\xi\,[1-\nu_{\text{efficacy}}]\,[\lambda_l + \sigma\,\lambda_h]\,X_{\{i=\text{LTBI},j,k,l\}}$$

reactivation:

$$\text{if } k \in \{\text{unvaccinated}, \text{vaccine} > 10\} \quad + \phi\; X_{\{i=\text{LTBI},j,k,l\}}$$

$$\text{if } k \in \{\text{vaccine} \leq 1, \ldots, \text{vaccine} \leq 10\} \quad + [1-\nu_{\text{efficacy}}]\,\phi\; X_{\{i=\text{LTBI},j,k,l\}}$$

treatment:

$$- [1-k]\,\omega\, X_{\{i,j,k,l\}}$$

aging and continuous vaccination:

$$\text{if } l \in \{0-9\} \quad - 0.1\, X_{\{i,j,k,l\}}$$

$$\text{if } l \in \{10-19\} \text{ and } k \in \{\text{unvaccinated}\} \quad - 0.1\, X_{\{i,j,k,l=10-19\}} + 0.1\,(1-\nu_{\text{coverage:V-10}})\, X_{\{i,j,k,l=0-9\}}$$

$$\text{if } l \in \{10-19\} \text{ and } k \in \{\text{vaccine} \leq 1\} \quad - 0.1\, X_{\{i,j,k,l=10-19\}} + 0.1\,\nu_{\text{coverage:V-10}}\, X_{\{i,j,k,l=0-9\}}$$

$$\text{if } l \in \{20+\} \quad + 0.1\, X_{\{i,j,k,l=0-9\}}$$

vaccine immunity:

$$\text{if } k \in \{\text{vaccine} \leq 1\} \quad - X_{\{i,j,k,l\}}$$

$$\text{if } k \in \{\text{vaccine} \leq 2, \ldots, \text{vaccine} \leq 10\} \quad + X_{\{i,j,k-1,l\}} - X_{\{i,j,k,l\}}$$

$$\text{if } k \in \{\text{vaccine} > 10\} \quad + X_{\{i,j,k-1,l\}}$$

migration:

$$\text{if } j \in \{\text{hotspot}\} \quad - m\, X_{\{i,j,k,l\}} + m\,\frac{N_h}{N_l}\, X_{\{i,j=\text{general population},k,l\}}$$

$$\text{if } j \in \{\text{general population}\} \quad + m\, X_{\{i,j=\text{hotspot},k,l\}} - m\,\frac{N_h}{N_l}\, X_{\{i,j,k,l\}}$$

Table S-1: Model parameters and inputs.

Model parameters/inputs	Symbols	Values Reference (Range)	References
Per capita mortality rate	μ	0.018 per year	-assumed-
Per capita mortality rate for individuals actively infected with TB	μ_A	0.2 per year 0.15-0.25	[4]
Fraction of infections that progress rapidly to active TB	p	0.14 0.1-0.2	[5]
Per capita reactivation rate	ϕ	0.001 per year 0.0005-0.002	[6]
Average duration of active TB until diagnosis and initiation of treatment	$1/\omega$	12 months 8-24	[7]
Percentage of TB cases with successful treatment	$1-k$	95% 85-97.5%	[7]
Relative hazard of reinfection in a host with LTBI	ξ	0.33 0.25-0.5	[8, 9, 10, 11]
Per capita transmission rates in hotspot general population	β_h β_l	variable (per infectious person-year) hotspot: 6.31-10.37 general population: 3.29-6.98	-fit to data-
Percentages of the population in hotspot and general population	N_h, N_l	10%, 90%	-assumed-
Total TB incidences in hotspot & general population	–	190, 125 per 100,000 per year	-data-
Migration; percentage of population that migrated within the last year	m	1% $(0-3\%)$	[3]
Mixing; percentage of shared contacts between hotspot & general population	σ	3% $(1-5\%)$	-assumed-
Vaccine efficacy, percentage protection against active TB	ν_{efficacy}	60% $(40-80\%)$	-assumed-
V-10 vaccine coverage, % receiving vaccine in hotspot and general population	$\nu_{\text{coverage:V-10}}$	80%,80%	-assumed-
V-A, untargeted, % receiving vaccine in hotpot and general population	–	8%,8%	-assumed-
V-A, spatially targeted, % receiving vaccine in hotpot and general population	–	80%,0%	-assumed-
Duration of vaccine-derived immunity on average	–	10 years	-assumed-

Model calibration

Model calibration was performed in two stages. First, we calibrated the demographic part of the model to generate the population age-distribution matching the data. This was achieved by fitting age-specific mortality rates such that the population age-distribution matched that of Gujarat, based on 2011 census. Specifically, the fractions of population in the age categories 0-9 years, 10-19 years, and 20 and older were 0.178, 0.187, and 0.635, respectively [2]. The fitting was performed within `R` [12], using optimization function `optim` with Nelder-Mead algorithm to mininize the squared difference between the data and the model fits.

After calibrating the demographic part of the model, we calibrated TB incidence. This was achieved by fitting TB transmission rates in "hotspots" (β_h) and the rest of the population (β_l) such that the TB incidence in the two sub-populations at equilibrium matched the data. Note that this calibration was performed separately for each set of mixing (σ) and migration (m) parameter values accounting for differences in implied transmission rates as a result of differences in mixing and migration. The fitting was performed within `R` [12], using optimization function `optim` with Nelder-Mead algorithm to mininize the squared difference between the data and the model fits.

Sensitivity analyses

Sensitivity to variation in migration rates

We varied annual migration rates between 0% to 3% per year (the baseline value used in the analyses in the main text was 1% per year), and assessed how these changes affected the roles of spatial heterogeneity and mixing in shaping the value of spatially targeted vaccination. As seen in Fig. Fig. S-5, the roles of spatial heterogeneity and mixing remained robust to variation in migration rates.

Sensitivity to variation in vaccine efficacy.

We explored sensitivity of the results to variation in vaccine efficacy. Compared to a vaccine efficacy of 60% used in the main text, here we explore scenarios with 40-80% vaccine efficacies (Fig. S-6). We find that the main results are fairly robust to some variation in vaccine efficacy. We do note that comparative benefit of spatially targeted vaccines may somewhat diminish when the vaccine efficacy increases (as can be seen in the relatively higher contours for 80% efficacy as opposed to 40%). This is because as vaccine efficacy increases, the likelihood of redundant vaccination (ie, vaccination of individuals that have vaccine derived protection from previous vaccine) increases when it is concentrated in smaller population.

Variation in the size of targeted "hotspot".

In our primary analysis of targeting, we considered a hotspot that consisted of the top 10% of the population with the highest TB incidence measured at the TU-level. These hotspots were targeted in the spatially targeted vaccination. Here we additionally explored scenarios where we considered hotspot that comprised of TU with top 5% of the highest incident population (5%-model), and top 20% of the highest incident population (20%-model). In the 5%-model, the TB incidence in the hotspot was 199.85 per 100,000 per year, and 127.8 per 100,000 per year in the remaining general population. We assumed that during the untargeted vacccination, 4% of the adults were vaccinated in both the hotspot and the general population. We assumed that during the spatially targeted vaccination, 80% of the adults were vaccinated in the hotspot and none in the general population. Hence, both strategies used the same number of vaccines. The augmentation in the impact of vaccination when the vaccined

were spatially targeted to these hotspots were 1.25-fold when top 5% of the population were targeted (Fig. S-7 [Left]), compared to 1.17-fold when top 10% were targeted.

In the 20%-model, the TB incidence in the hotspot was 176.35 per 100,000 per year, and 120.165 per 100,000 per year in the remaining general population. We assumed that during the untargeted vacccination, 16% of the adults were vaccinated in both the hotspot and the general population. We assumed that during the spatially targeted vaccination, 80% of the adults were vaccinated in the hotspot and none in the general population. Hence, both strategies used the same number of vaccines. The augmentation in the impact of vaccination when the vaccined were spatially targeted to these hotspots were 1.09-fold when top 20% of the population were targeted (Fig. S-7 [Right]), compared to 1.17-fold when top 10% were targeted.

Sensitivity to vaccine coverage.

To explore the sensitivity of the outcomes to level of vaccine coverage, we varied the level of adult-vaccine coverage in the hotspot during STV between 0 to 100% (and no vaccination in the general population). Note that the level of coverage in the in the entire population for corresponding UTV would be 1/10 of the coverage level in the hotspot to ensure that STV and comparable UTV used the same number of vaccines. The augmentation in the impact of vaccination achieved by STV over UTV are plotted for populations with different levels of mixing, and different levels of vaccine coverage in Fig. S-8. The value of targeting marginally diminishes as the coverage increases, and the begins to decrease. The level of coverage at which the marginal value stops increasing depends on the degree of mixing between the hotspot and the general population: lower the degree of mixing, lower the level of coverage at which the marginal value stops increasing.

Continuation and discontinuation of vaccination.

We explored the patterns of reduction in TB incidence in the scenarios where the vaccination is either continued beyond 20 years (Fig. S-9[Left]), or discontinued after 20 years of vaccination (Fig. S-9[Right]). The effect of vaccination on TB incidence stabilized after 20 years, and when the vaccination was continued beyond the initial 20 years, we found that the relative benefit of spatial targeting persisted. When the vaccination was discontinued, the effect on TB incidence subsided in the next 20 years such that the TB incidence returned to the levels prior to the vaccination.

Vaccine delivery and TB risk

In our main model, we assumed that individuals received vaccines independent of their TB risk. Here we explored the two scenarios where the vaccine delivery correlated with TB risk. In the first scenario vaccine delivery was skewed towards individuals with lower risk of TB. To model this, we assumed that during the periodic adult vaccine campaigns (V-A) uninfected individuals in both sub-populations were 25% more likely to receive the vaccine (compared to the main scenario where the vaccine distributions were independent of TB risk). The total number of vaccines delivered was held to the same number as in the main scenario to allow comparisons between them. In the second scenario vaccine delivery was skewed towards individuals with higher risk of TB. To model this, we assumed that during the periodic adult vaccine campaigns (V-A) individuals with latent TB infection (in both sub-populations) were 25% more likely to receive the vaccine (compared to main scenario where vaccine distributions were independent of TB risk). Again, the total number of vaccines delivered was held to the same number as in the main scenario. We found that skewing the vaccine delivery in either direction resulted in minimal differences to the main results (Fig. S-9).

Multivariate sensitivity analyses

To assess the sensitivity of the primary result—the relative reduction in TB incidence 10 years after vaccination that was spatially targeted compared to a vaccination that was untargted— to variability in TB natural history parameters, we also carried out multivariate sensitivity analyses. Using the reference scenario as the baseline, we conducted 5,000 simulations in which all TB natural history parameter values were simultaneously varied uniformly across ranges (as provided in Figure. S-14) using Latin Hypercube Sampling. The distribution of TB heterogeneity (ratio of TB incidence in the "hotspots" to the remaining population) in the simulations are shown in Fig. S-4[Left]. Additionally, we sampled 1000 parameter sets from the given parameter ranges, and simulated the models without the vaccine to estimate the incidences in the hotspots and the general population (See Fig. S-4[Left]). Using these simulations, we assessed the sensitivity of the primary results in the reference scenario to variation in these parameters. In particular, we used the estimates corresponding to 2.5^{th} and 97.5^{th} percentile of all simulation results to construct 95% uncertainty ranges in our estimates.

The median reduction in TB incidences 10 years after an untargeted vaccination was 24.9% [95% range: 12.3% - 35.2%] (Fig. S-11[Left, blue histogram]). In comparison, spatially targeted vaccination resulted in a median reduction of 29.5% [95% range: 15.0% - 44.4%] (Fig. S-11[Left, red histogram]). As a result, spatially targeted vaccination was 1.21 times [95% range: 1.11 - 1.33] more effective than untargeted vaccination in reducing TB incidence (Fig. S-11[Right])

These results were robust to the choice of distribution according to which the parameters were sampled. When triangular distributions were used instead of uniform, each with the same range as for the uniform and with the mode equal to the base parameter value, the median reductions in TB incidences 10 years were 25.2% [95% range: 14.8% - 32.9%] (Fig. S-12[Left, blue histogram]) when the vaccine was untargeted, and 30.1% [95% range: 18.3% - 40.5%] (Fig. S-12[Left, red histogram]) when the vaccine was targeted. Spatially targeted vaccination was 1.21 times [95% range: 1.12 - 1.28] more effective than untargeted vaccination in reducing TB incidence (Fig. S-12[Right])

We also calculated partial ranked correlation coefficients (PRCC), comparing each parameter value with comparative reduction in tuberculosis (TB) incidence after 10 years of vaccination that was spatially targeted vaccination and untargeted vaccination. The low levels of PRCCs for all parameters except ξ, relative probability of reinfection among LTBI, suggest that the results are mostly very robust to changes in the natural history parameters (Fig. S-14). Relative probability of reinfection among LTBI, ξ, was positively correlated with the relative value of STV. This is likely because, increase in this reinfection probability, is likely to accentuate the disparity in TB incidence between hotspots and the general population. This in turn will increase the value of STV, since STV is more effective when there is stronger heterogeneity.

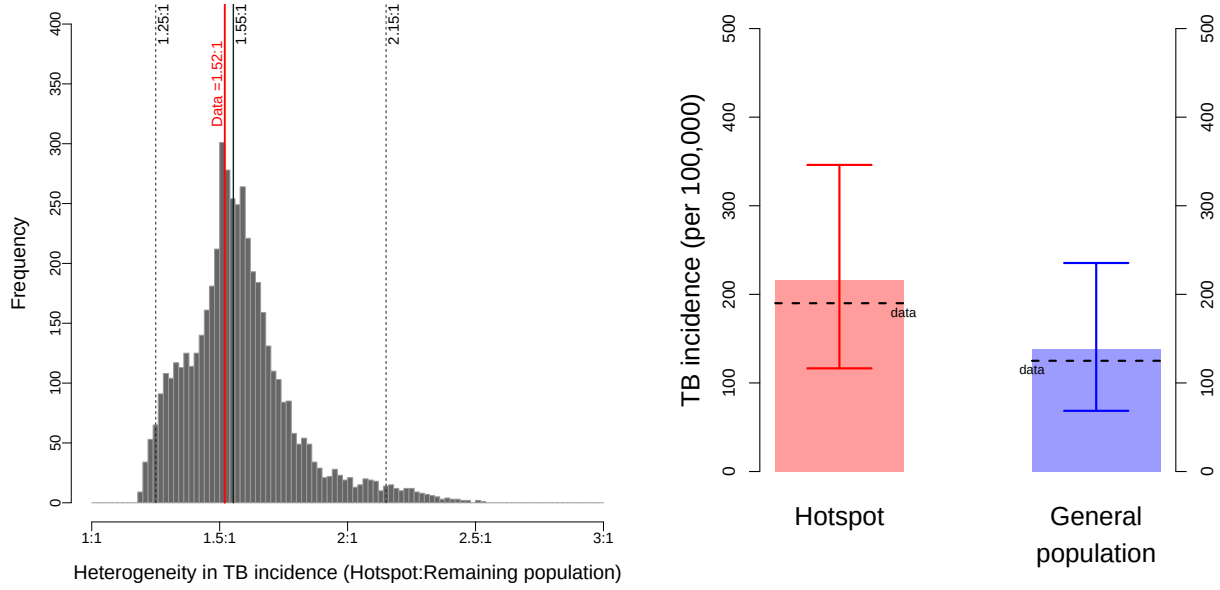

Figure S-4: Uncertainty analysis: TB heterogeneity and TB incidence [left] Shown are distribution of TB heterogeneity (ratio of TB incidence in the "hotspots" to the remaining population) in 5000 simulations conducted for uncertainty analyses. The solid black line indicates the median, and the two dashed lines indicate the 95% range. The heterogeneity in Gujarat data is indicated by the solid red line. [Right] Shown are medians (box) and the interquartile ranges (bars) of TB incidences in the hotspots and the general population in 1000 simulations sampled from the given parameter ranges.

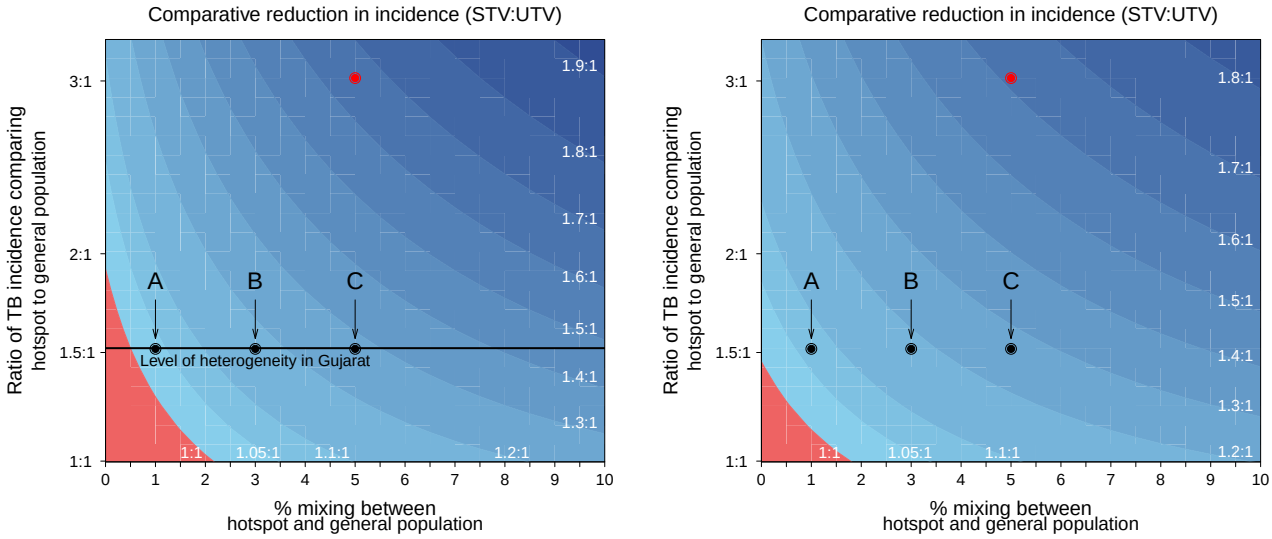

Figure S-5: Variation in migration rates. We explore the effect of heterogeneity (vertical axis) and mixing (horizontal axis) at different migrations rates: [left] No migration; and [Right] Annual migration rate of 3%. These figures are comparable to Fig. 4 in the main text, where the annual migration rate is taken to be 1%. The marked red points represent scenarios in which the hotspot has three times the TB incidence of the general population, and shares 5% of all respiratory contacts with the general population.

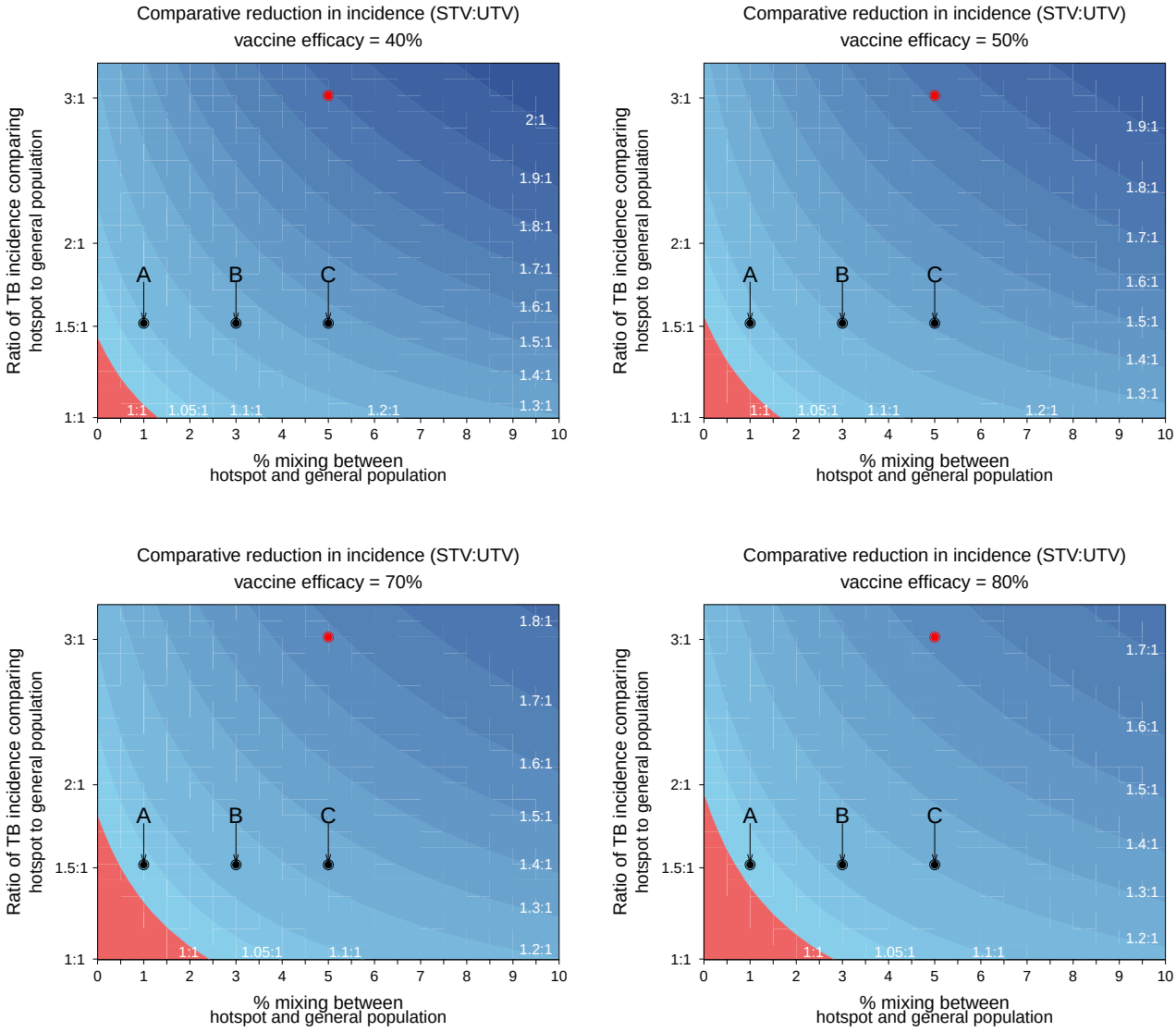

Figure S-6: Variation in vaccine efficacy. We explore the effect of heterogeneity (vertical axis) and mixing (horizontal axis) at different migrations rates: [Top-left] Vaccine efficacy is 40%; [Top-right] 50%; [Bottom-left] 60%; and [Bottom-right] 70%. These figures are comparable to Fig. 4 in the main text, where the vaccine efficacy is 60%. The marked red points represent scenarios in which the hotspot has three times the TB incidence of the general population, and shares 5% of all respiratory contacts with the general population.

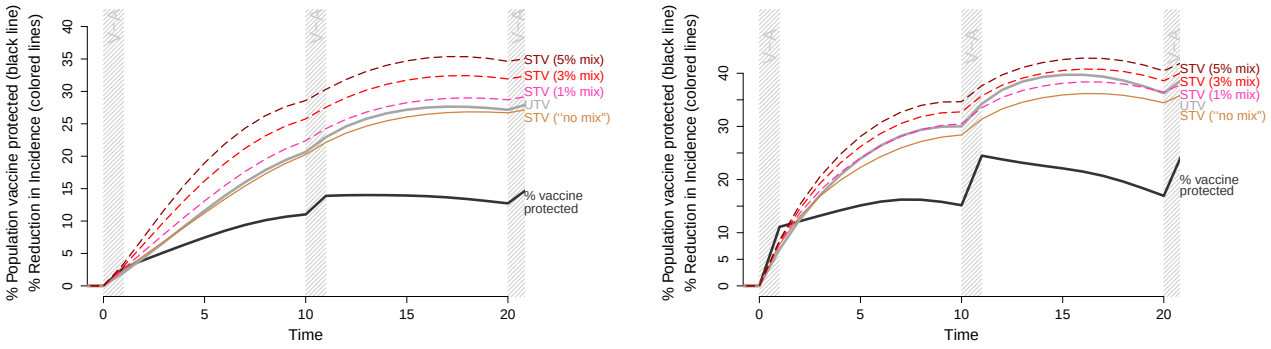

Figure S-7: Variation in the size of targeted hotspot. Reduction in TB incidence achieved through spatially targeted (STV) and untargeted (UTV) vaccination, where the vaccination campaign targets [Left] TUs comprising of the top 5% of highest TB incidence; or [Right] TUs comprising of the top 20% of highest TB incidence. As in Fig. 3 in the main text, plotted in black is the percentage of the population estimated to be vaccine-protected in the first 20 years after the deployment of the vaccine. The vaccine campaigns consist of two parts: (i) continuous vaccination of adolescents that turn 10 years old (V-10) at 80% coverage; and (ii) periodic vaccination of adults older that 20 years old (V-A) at 8% coverage (indicated by the hatched area). Plotted in color are the corresponding percentage reductions in TB incidence through the first 50 years after vaccine introduction in 5 different scenarios: (i) untargeted vaccination (UTV, in grey) and spatially targeted vaccination (STV) with: (ii) no migration and mixing ("no mix", in solid tan); (iii) annual migration at 1% and mixing at 1% (1% mix, in dashed pink); (iv) annual migration at 1% and mixing at 3% (3% mix, in dashed red); and (v) annual migration at 1% and mixing at 5% (5% mix, in dashed brown).

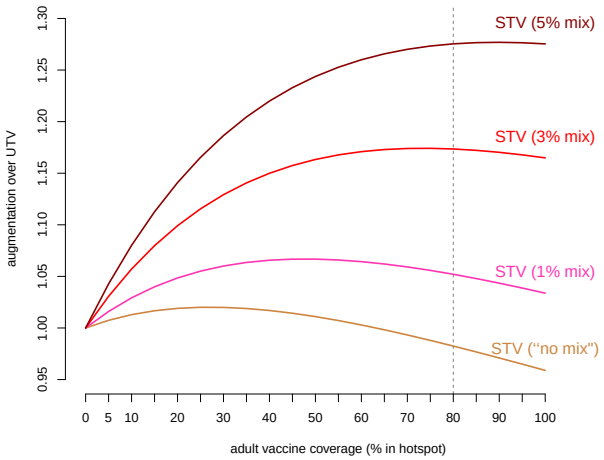

Figure S-8: Sensitivity to level of vaccine coverage Shown are augmentation in the impact of vaccination achieved by STV over UTV (vertical axis), for different levels of adult vaccine coverage (horizontal axis). The four lines represent four different levels of mixing between the hotspot and the general population. Note that the level of adult vaccine coverage in the baseline scenario was 80% (indicated by the dashed line).

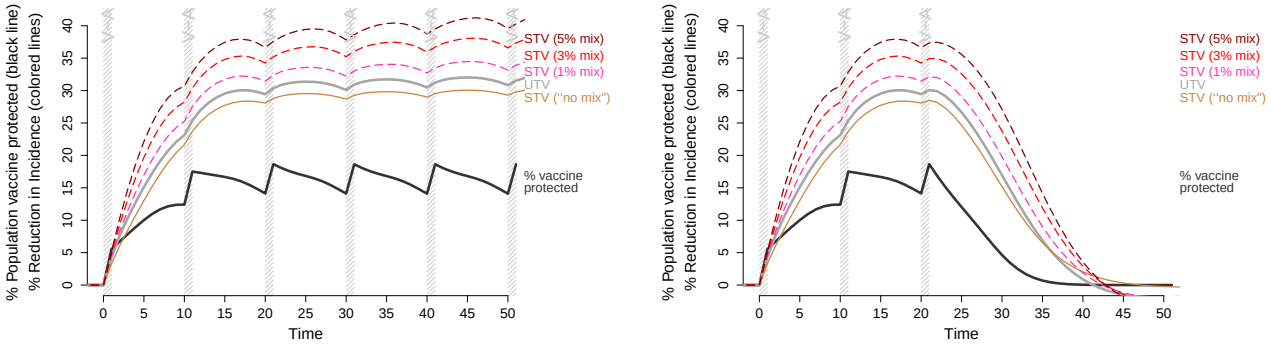

Figure S-9: Continuation and discontinuation of vaccination. Reduction in TB incidence achieved through spatially targeted (STV) and untargeted (UTV) vaccination, where the vaccination campaign is [Left] continued beyond the 20 years; or [Right] discontinued after 20 years of vaccination. As in Fig. 3 in the main text, plotted in black is the percentage of the population estimated to be vaccine-protected in the first 20 years after the deployment of the vaccine. The vaccine campaigns consist of two parts: (i) continuous vaccination of adolescents that turn 10 years old (V-10) at 80% coverage; and (ii) periodic vaccination of adults older that 20 years old (V-A) at 8% coverage (indicated by the hatched area). Plotted in color are the corresponding percentage reductions in TB incidence through the first 50 years after vaccine introduction in 5 different scenarios: (i) untargeted vaccination (UTV, in grey) and spatially targeted vaccination (STV) with: (ii) no migration and mixing ("no mix", in solid tan); (iii) annual migration at 1% and mixing at 1% (1% mix, in dashed pink); (iv) annual migration at 1% and mixing at 3% (3% mix, in dashed red); and (v) annual migration at 1% and mixing at 5% (5% mix, in dashed brown).

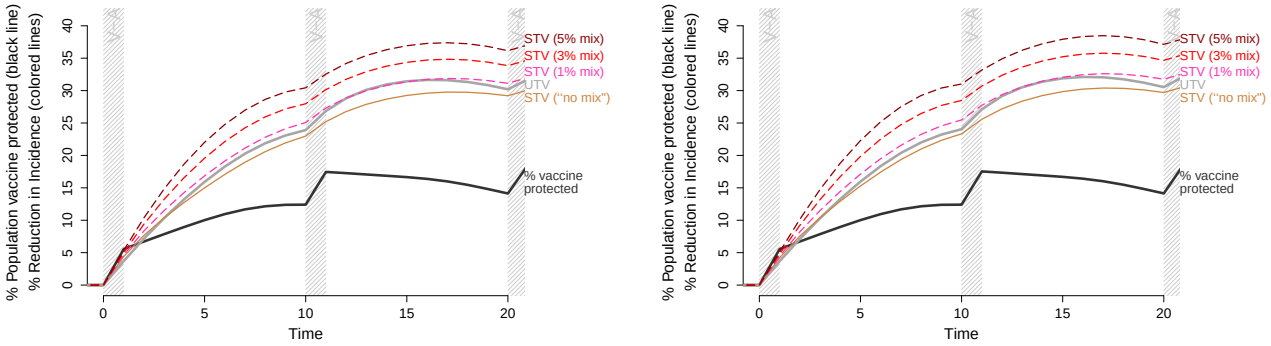

Figure S-10: Vaccine delivery and TB risk. Reduction in TB incidence achieved through spatially targeted (STV) and untargeted (UTV) vaccination, where the vaccine delivery is skewed towards individuals with [Left] lower risk of TB; or [Right] higher risk of TB. As in Fig. 2 in the main text, plotted in black is the percentage of the population estimated to be vaccine-protected in the first 20 years after the deployment of the vaccine. The vaccine campaigns consist of two parts: (i) continuous vaccination of adolescents that turn 10 years old (V-10) at 80% coverage; and (ii) periodic vaccination of adults older that 20 years old (V-A) at 8% coverage (indicated by the hatched area). Plotted in color are the corresponding percentage reductions in TB incidence through the first 50 years after vaccine introduction in 5 different scenarios: (i) untargeted vaccination (UTV, in grey) and spatially targeted vaccination (STV) with: (ii) no migration and mixing ("no mix", in solid tan); (iii) annual migration at 1% and mixing at 1% (1% mix, in dashed pink); (iv) annual migration at 1% and mixing at 3% (3% mix, in dashed red); and (v) annual migration at 1% and mixing at 5% (5% mix, in dashed brown).

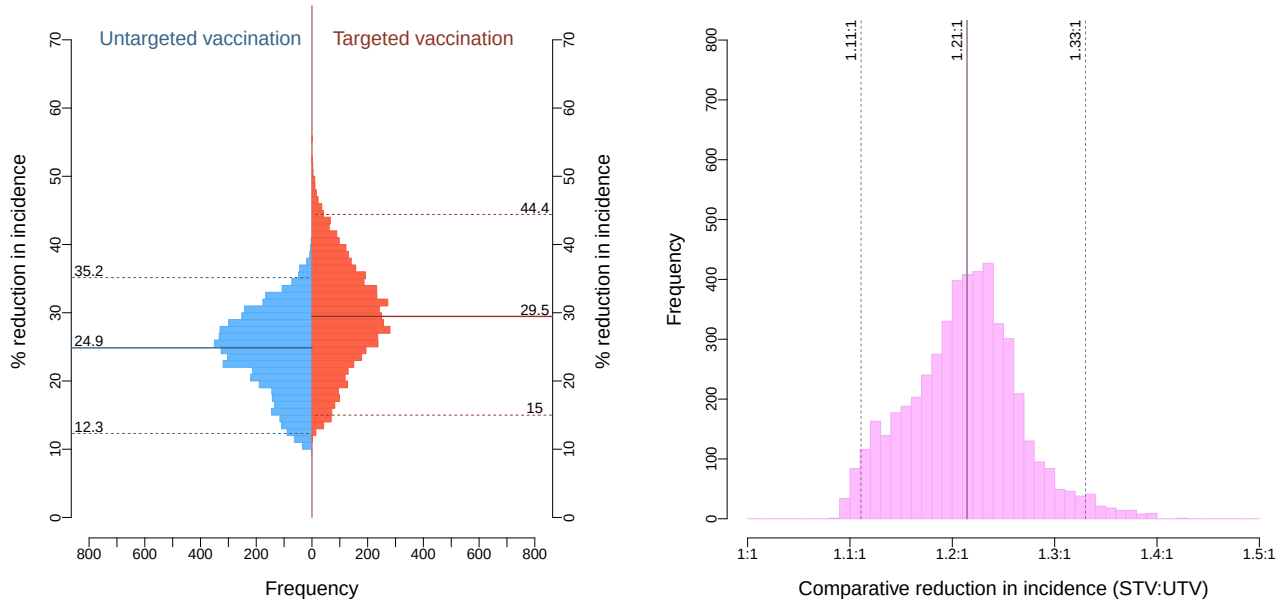

Figure S-11: Sensitivity to changes in TB natural history parameters. [Left] Frequency distributions of percentage reduction in TB incidences after 10 years of vaccination from an untargeted vaccination (blue histograms on the left) and spatially targeted vaccination (red histograms on the right). [Right] Resulting frequency distributions of comparative reduction in TB incidence as result of STV relative UTV. Also marked in the figures are the medians and 95% intervals for respective strategies.

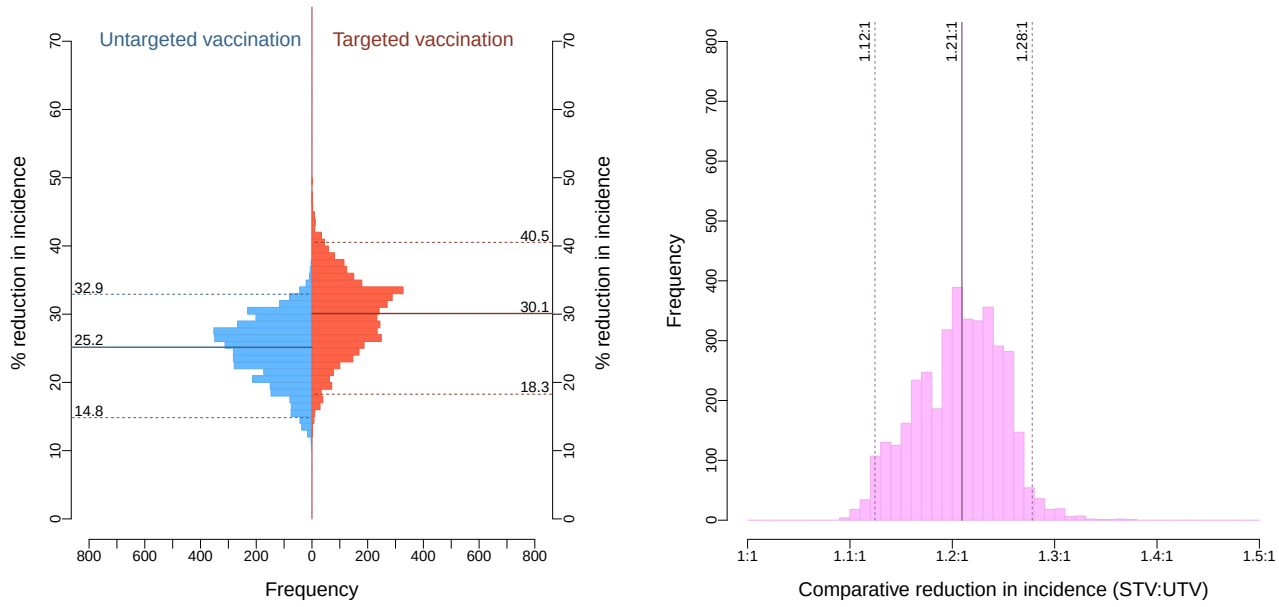

Figure S-12: Sensitivity to changes in TB natural history parameters; parameters drawn from triangular distributions. [Left] Frequency distributions of percentage reduction in TB incidences after 10 years of vaccination from an untargeted vaccination (blue histograms on the left) and spatially targeted vaccination (red histograms on the right). [Right] Resulting frequency distributions of comparative reduction in TB incidence as result of STV relative UTV. Also marked in the figures are the medians and 95% intervals for respective strategies. This figure is comparable to Fig. S-11, except here the parameters are drawn from triangular distributions.

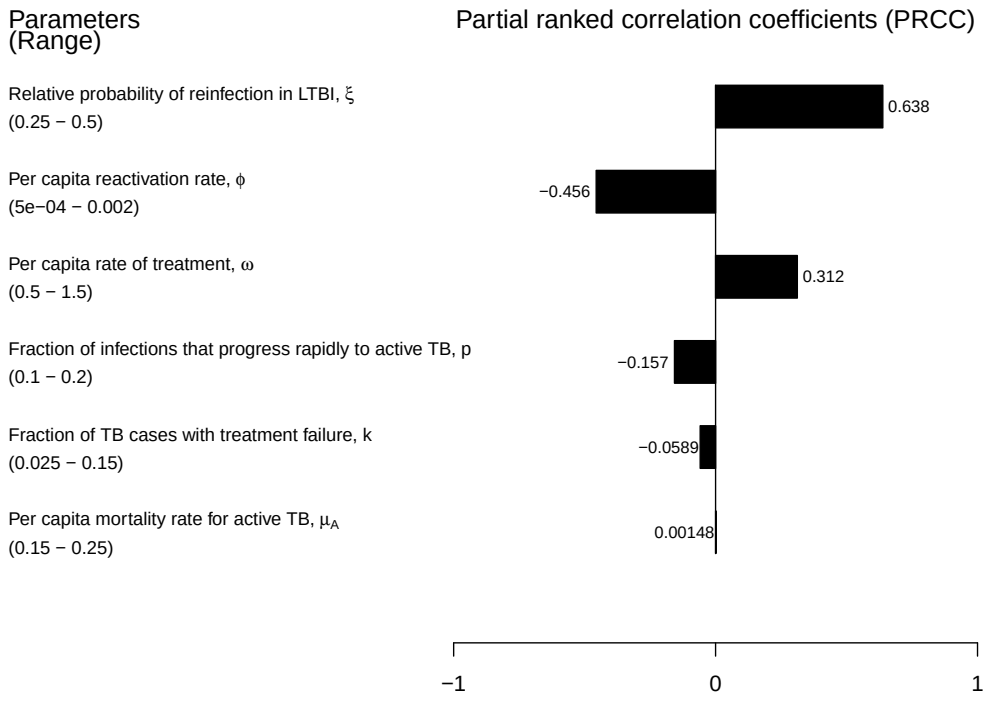

Figure S-13: Multivariable sensitivity analysis. Partial rank correlation coefficients (shown on the x axis) describe the degree of correlation between the corresponding parameter and comparative reduction in tuberculosis (TB) incidence after 10 years of vaccination that was spatially targeted vaccination and untargeted vaccination.

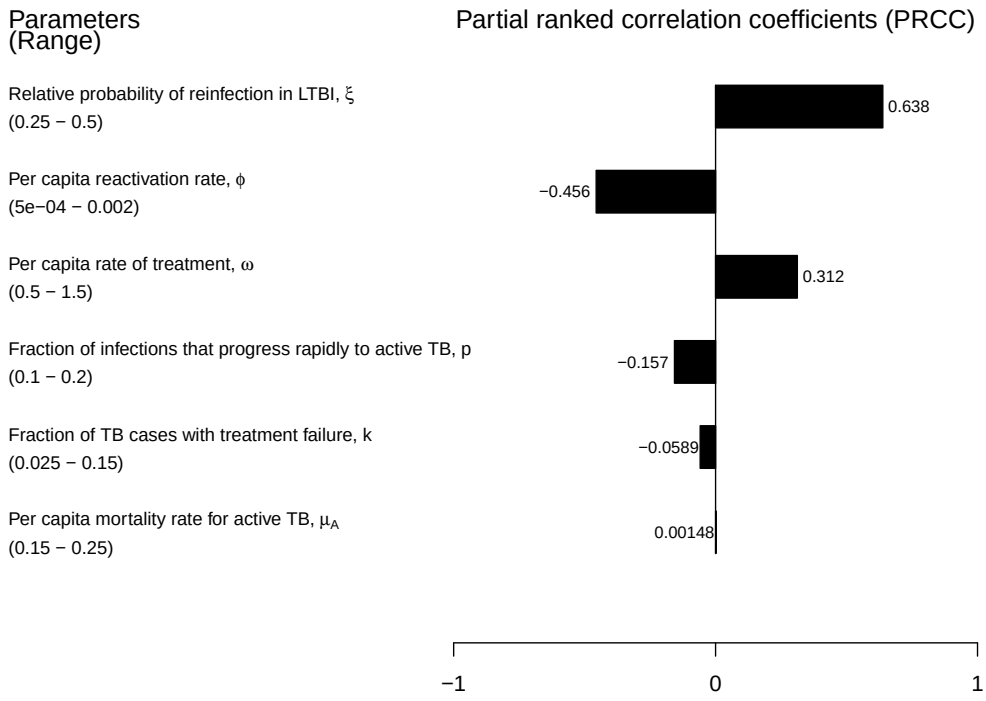

Figure S-14: Multivariable sensitivity analysis. Partial rank correlation coefficients (shown on the x axis) describe the degree of correlation between the corresponding parameter and comparative reduction in tuberculosis (TB) incidence after 10 years of vaccination that was spatially targeted vaccination and untargeted vaccination.

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